Remifentanil patient-controlled analgesia for labor – monitoring of newborn heart rate, blood pressure and oxygen saturation during the first 24 hours after delivery

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Submitted: 15 September 2011
Accepted: 8 February 2012

Arch Med Sci 2013; 9, 4: 697–702
DOI: 10.5114/aoms.2012.31306
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Abstract

Introduction: There is no available information about the effects of remifentanil labor analgesia on newborns' vital signs in the first hours after delivery. The aim of the study was to assess changes in the heart rate, blood pressure and oxygen saturation during the first 24 h of neonatal life after using remifentanil patient-controlled analgesia (PCA) for labor analgesia.

Material and methods: Forty-four full-term neonates, 23 from intravenous PCA remifentanil labor anesthesia 0.2 µg/kg, repeated not more frequently than every 2 min, and 21 born to mothers without any pharmacological forms of analgesia, were studied. Heart rate, oxygen saturation, and systolic (SBP) and diastolic blood pressure (DBP) were monitored using a Nellcor Oxi Max monitor N5500 (Tyco Healthcare), and recorded at 1 h, 6 h, 12 h and 24 h.

Results: No significant differences in heart rate ($p = 0.54$; $p = 0.26$; $p = 0.60$; $p = 0.83$), oxygen saturation ($p = 0.21$; $p = 0.27$; $p = 0.61$; $p = 0.9$) and DBP ($p = 0.98$; $p = 0.31$; $p = 0.83$; $p = 0.58$) between the groups at 1 h, 6 h, 12 h and 24 h. Newborns from the remifentanil group had lower SBP at 1 h of life (59 mm Hg vs. 68.5 mm Hg) but the difference was just on the borderline of statistical significance ($p > 0.06$). There were no significant differences in SBP between the groups at 6 h ($p = 0.65$), 12 h ($p = 0.11$), and 24 h ($p = 0.89$) of life.

Conclusions: Remifentanil PCA analgesia during labor does not significantly modify the oxygen saturation, heart rate and blood pressure in infants during the first day of their life. Therefore, further studies are needed to explain the observed trend for arterial hypotension in the first hour of life in infants born to mothers treated with remifentanil.

Key words: labor pain, opioids, neonatal outcome.

Introduction

Remifentanil is a rapid-acting synthetic µ-opioid receptor agonist with a very short half-life, that is quickly metabolized by plasma and tissue esterases, regardless of any hepatic or renal impairment, or age-related differences in half-life [1-3].

For a decade, anesthesiologists have used the unique properties of remifentanil in the settings of surgical anesthesia, sedation and postoperative analgesia since its introduction into labor analgesia. However,

remifentanil is not licensed to be administered to pregnant women. As it stands remifentanil is the best opioid for obstetric use so far. Proper informed consent, appropriate monitoring of the mother and the newborn, one-to-one nursing or midwifery care, as well as the availability of an attending physician experienced in neonatal resuscitation and an anesthesiologist with experience in the use of remifentanil, are important to ensure that this method retains its credit for obstetric analgesia [4].

Remifentanil rapidly and extensively crosses the placenta (umbilical vein/maternal artery ratio 0.88) in term pregnancies [5]. It is believed that although remifentanil crosses the placenta, it is eliminated quickly in neonates by rapid metabolism or redistribution. However, because of different duration of labor, pain severity and subjective feeling, total doses of remifentanil transferred during patient-controlled analgesia to the fetus/newborn may differ significantly. The phenomenon of the individual sensitivity to the drug and accumulation in some patients should also be taken into consideration. In general, the pharmacokinetics of opioids during fetal life and in newborns is guided by maturational aspects of absorption, distribution, metabolism and elimination of these drugs. In this age range, important factors such as gestational age, body composition, weight, liver maturation and impaired renal function result in considerable individual variability in the pharmacokinetics of the majority of drugs [6, 7].

There are limited studies about the safety of remifentanil use as a bolus in induction of general anesthesia for caesarean delivery [8–11]. In very few studies maternal and neonatal side-effects of remifentanil patient-controlled analgesia in labor are described [4, 11–14]. Cardiovascular instability and respiratory depression immediately after birth were noticed in some cases. In papers published up to now only Apgar score results, umbilical blood gas analysis or muscle rigidity during the first 10 min after birth were used as indicators of newborn well-being after remifentanil labor analgesia. In one study performed by Draisci *et al*., neonates were observed in the nursery with SpO_2 monitoring removed at 3 h after birth [11]. None of the papers reports monitoring of the heart rate, oxygen saturation and blood pressure performed for at least 24 h after birth.

The aim of the study was to assess changes in the heart rate, blood pressure and oxygen saturation of hemoglobin during the first 24 h of life in neonates born after using remifentanil PCA for labor analgesia in comparison with neonates born after labor without any pharmacological analgesia.

Material and methods

Patients

The study included 44 infants born at the Department of Obstetrics and Gynecology, and then hospitalized at the Department of Neonatology, Pomeranian Medical University in Szczecin, Poland. All infants were from uncomplicated pregnancies and after a normal spontaneous vaginal delivery.

Enrollment in the study was as follows: Remifentanil PCA for labor was suggested to pregnant women with no known obstetric complications and contraindications to epidural analgesia or in cases when the mother rejected the idea of regional analgesia. Neonates from the mothers who accepted remifentanil analgesia comprised the study group, while neonates from mothers who refused any pharmacological method of analgesia constituted the control group.

Inclusion criteria for the remifentanil group:

- written informed maternal consent for labor analgesia with the remifentanil PCA method obtained before enrollment of the newborn;
- no complications during pregnancy;
- healthy pregnant women;
- term pregnancy.

Inclusion criteria for the control group:

- written informed maternal consent for refusal of labor analgesia with remifentanil PCA method obtained before enrollment of the newborn;
- no pharmacological agents of labor pain release used during labor;
- no complications during pregnancy;
- healthy pregnant women;
- term pregnancy.

Exclusion criteria for both groups:

- major congenital malformations (cardiac, central nervous system, respiratory tract, chromosomal abnormalities and all lethal malformations);
- early onset sepsis (recognized up to 72 h of life based on clinical symptoms, laboratory test and bacterial culture results).

The remifentanil group consisted of 23 newborns of mothers who received intravenous remifentanil anesthesia using the method of analgesia controlled by the patient (PCA – patient-controlled analgesia) at the dose of 0.2 µg/kg repeated not more frequently than every 2 min. No background infusions of remifentanil were used. The control group comprised 21 infants born to mothers who did not use any pharmacological forms of anesthesia.

Methods

The study was designed as a prospective clinical controlled trial, conducted in compliance with the Declaration of Helsinki principles. The protocol and the parental informed consent forms were approved by the institutional review board (Ethical Committee of the Pomeranian Medical University, Szczecin, Poland). Written informed consent of the mother for examinations of the child was obtained in each study case.

All neonates were observed in the nursery for at least 48 h after birth with transcutaneous O_2 saturation (ScO_2) monitoring during 24 h after delivery. Measures of the heart rate (HR) and blood pressure (BP) of the newborns were recorded four times during the first day of life, at 1 h, 6 h, 12 h and 24 h. Vital signs such as the heart rate, transcutaneous O_2 saturation of hemoglobin and blood pressure were monitored using a Nellcor Oxi Max monitor N5500 (Tyco Healthcare). Results of measurements of ScO_2, HR and BP obtained at 1 h, 6 h, 12 h and 24 h of life were statistically analyzed.

Statistical analysis

The distribution of continuous variables was tested for normality by the Shapiro-Wilk test. The differences between newborns from the remifentanil PCA labor analgesia group and controls were tested by the Wilcoxon test or Mann-Whitney nonparametric *U* test as appropriate. Values were presented as mean and standard deviation or median and ranges, as appropriate. A value of $p < 0.05$ was considered statistically significant.

Results

General characteristics of the analyzed groups of newborns are presented in Table I. No significant differences regarding the number of patients enrolled, sex of newborns, gestational age and birth weight between newborns from the compared groups were found (Table I). However, 5-minute Apgar score was significantly lower in the remifentanil than in the control group (Table I).

Five newborns from the remifentanil group (21.7%) needed respiratory support with an oxygen bag and mask at the delivery room. Three of those demanded an oxygen hood also during the first hours of life, meaning that respiratory depression in newborns can develop after remifentanil used as a PCA method for labor analgesia.

There were no significant differences in ScO_2 values recorded at 1 h, 6 h, 12 h, and 24 h of life between the compared groups of newborns (Table II).

There was no significant difference in the heart rate (HR) values recorded during the 24-hour monitoring of newborns at 1 h, 6 h, 12 h, and 24 h of life between newborns from the compared groups (Table III).

The neonates from the remifentanil group had lower systolic blood pressure in the first hour of life compared to the values found in newborns from the control group but the difference was only on the borderline of statistical significance ($p > 0.06$) (Table IV).

There were no significant differences in the diastolic blood pressure values recorded at 1 h, 6 h, 12 h,

Table I. General characteristics of participants

Variable	Remifentanil group	Control group	Statistical analysis
Number of patients	23	21	NS
Female sex	7 (30.43%)	11 (52.38%)	NS
Male sex	16 (69.57%)	10 (47.62%)	NS
Duration of pregnancy [weeks]*	35–41 (39.04 ±1.74)	37–41 (38.9 ±1.28)	NS
Birth weight [g]*	2550–4180 (3324.8 ±443.4)	2400–4000 (3366.7 ±416.1)	NS
5' Apgar score, median (range)	9 (8-10)	10 (9-10)	$p < 0.001$

**Values are presented as ranges and mean ± standard deviation*

Table II. Comparison of oxygen saturation by pulse oximetry values (ScO_2) recorded in newborns from the remifentanil and the control group at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median ScO_2	Minimum ScO_2	Maximum ScO_2	Q25%	Q75%	Value of *p**
Remifentanil	1	23	97.0	90	100	96	100	0.20796
Control	1	21	98.0	90	100	97.5	98.5	
Remifentanil	6	23	98.0	94	100	96	98	0.27885
Control	6	21	98.0	92	100	97	99	
Remifentanil	12	23	98.0	96	100	97	99	0.61449
Control	12	21	99.0	94	100	97	100	
Remifentanil	24	23	98.5	96	100	97	100	0.86997
Control	24	21	98.5	96	100	97.5	99.5	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

Table III. Comparison of the heart rate (HR) values in beats per minute (bpm) in newborns from the remifentanil and the control group obtained at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median HR [bpm]	Minimum HR [bpm]	Maximum HR [bpm]	Q25%	Q75%	Value of *p**
Remifentanil	1	23	138.0	127	180	130	149	0.54557
Control	1	21	142.0	130	161	137	145.5	
Remifentanil	6	23	138.5	103	155	131	142	0.26242
Control	6	21	140.5	122	159	133.5	147	
Remifentanil	12	23	136.0	110	173	127	148	0.60566
Control	12	21	138.0	118	153	132	145	
Remifentanil	24	23	139.0	123	160	134	148	0.83050
Control	24	21	141.0	107	167	135	147.5	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

Table IV. Comparison of systolic blood pressure (SBP) values in newborns from the remifentanil and the control group at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median SBP	Minimum SBP	Maximum SBP	Q25%	Q75%	Value of *p**
Remifentanil	1	23	59.0	49	97	52	67	0.06949
Control	1	21	68.5	36	90	61	76	
Remifentanil	6	23	68.0	51	100	54	73	0.65591
Control	6	21	65.0	42	98	60	74	
Remifentanil	12	23	60.0	53	81	58	75	0.11315
Control	12	21	64.0	50	93	61	81	
Remifentanil	24	23	66.0	41	85	64	72	0.89497
Control	24	21	64.5	52	95	60	76	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

Table V. Comparison of diastolic blood pressure (DBP) values in newborns from the remifentanil and the control group at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median DBP	Minimum DBP	Maximum DBP	Q25%	Q75%	Value of *p**
Remifentanil	1	23	36.0	21	56	29	40	0.98683
Control	1	21	34.0	24	55	31	41	
Remifentanil	6	23	38.0	23	69	32	41	0.31411
Control	6	21	32.0	20	64	25	50	
Remifentanil	12	23	35.0	25	44	32	39	0.83013
Control	12	21	32.0	22	52	30	44	
Remifentanil	24	23	40.0	23	67	35	46	0.58605
Control	24	21	38.0	22	53	33	44	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

and 24 h of life between both groups of newborns (Table V).

Discussion

During childbirth, remifentanil offers hemodynamic stability for the mother, even during general anesthesia, but 50% of newborns may require ventilatory assistance because of respiratory depression. There is also a case report of generalized rigidity and apnea in a neonate immediately after birth following remifentanil administration during caesarean section to a high-risk mother [15]. Therefore, supervision and monitoring of both the mother and the infant are necessary [15].

To the best of our knowledge, this is the first published report on the biophysical monitoring of the heart rate, pulse oximetry and blood pressure during the first 24 h after birth in neonates born to PCA remifentanil labor analgesia mothers. We found no

differences in the heart rate, pulse oximetry, or systolic and diastolic blood pressure values between the group of newborns born to remifentanil PCA labor analgesia women and the group of newborns born to control women, except for non-significant hypotension (systolic blood pressure below 60 mm Hg in the remifentanil group) at 1 h after delivery.

Despite a very short half-life in some adult patients, remifentanil was reported to possibly cause side effects even 1 h after stopping the infusion [16]. Based on the limited number of studies on newborns, one may consider that the varied process of birth (interruption of the mother-fetus metabolism), comorbidities, environmental factors (e.g. maternal smoking, use of medications) and polymorphisms contribute to the individual variability related to the pharmacokinetics of opioids, including remifentanil, in the neonatal period [6, 17].

Arnal *et al*. carried out a systematic review on the use of remifentanil in childbirth analgesia [18]. In the majority of cases, no serious side effects for either mothers or neonates in the delivery room conditions were noted. The authors concluded that intravenous remifentanil may be the drug of choice for childbirth analgesia when regional analgesia techniques are contraindicated [18].

Therefore, in papers published up to now, information about the effects of remifentanil labor analgesia on newborns' vital signs in the first hours after delivery is scarce.

Only in the study of Draisci *et al.* were neonates observed for at least 24 h after birth in the nursery, with SpO_2 monitoring removed at 3 h if no episodes of desaturation had occurred [11]. Draisci reported significantly lower Apgar scores at 1 min and 5 min after birth and respiratory depression after using remifentanil 0.5 µg/kg as a bolus in cesarean section under general anesthesia [11]. They concluded that even at low doses remifentanil has the potential to cause respiratory depression. No other adverse effects during the first 24 h of neonatal life were observed in their study [11].

The ideal regimen for remifentanil infusion is yet to be established and further studies on maternal and fetal safety need to be carried out. During our study project, the dose of 0.2 µg/kg repeated not more frequently than every 2 min with no background infusion of remifentanil was used. Such doses seem to be safe from the fetal/neonatal point of view [4]. Additional information about the doses safe for neonates may be found in reports on the use of remifentanil in neonatal intensive care and anesthetic practice [6]. Lago *et al*. recorded the number of clinically significant desaturations, apnea and hypotension for the first 3 h after the infusion of remifentanil 0.03 µg/kg/min was over [1].

In a study by Wee *et al*., the starting rate of 0.025 µg/kg/min was considered preferable to avoid bradycardia and hypotension that were observed after administration of either a bolus of 1 µg/kg or an infusion rate of 1 µg/kg/min [19]. In a double-blinded, randomized and prospective study of Chambers, clinically insignificant bradycardia and mild hypotension (with no repercussion on peripheral perfusion) frequently followed administration of remifentanil 1 µg/kg/min or saline as a bolus over 1 min [20].

Davis *et al*., and Galinkin *et al*., among 60 patients with a mean rate of remifentanil infusion of 0.55 µg/kg/min, noticed the necessity of hypotensive treatment (systolic blood pressure < 60 mm Hg) in 11% of the patients [2, 3].

In a pilot study, INSURE, with remifentanil 2 µg/kg infused over 60 s, mean blood pressure decreased 5 min after remifentanil application, and usually normalized within 20-30 min after remifentanil infusion [21]. Hypothetically, remifentanil PCA labor analgesia may negatively influence the newborn condition even up to 30 min after birth. It should also be taken into account that higher remifentanil doses are associated with an increased risk of side effects. In the year 2010, Standing *et al*., published a study about the relationship between whole blood remifentanil concentration and its hypotensive effects in infants undergoing cranioplasty [22]. They concluded that remifentanil is effective in causing arterial hypotension.

Summarizing the above data and our results, hypotension after remifentanil infusion can occur. Further trials are needed to evaluate ideal dosing regimens and combinations of agents to be used with remifentanil in labor analgesia.

Our study has some limitations, chief among them the studied problem itself, whether or not to give labor analgesia. From an ethical point of view, a randomized, blinded study of used or not used labor analgesia is not accepted in pregnant women during labor. Also, it is commonly known that some pregnant women prefer to have natural labor without any pharmacological analgesia. Therefore, in our study the choice of whether to use labor analgesia or refuse it belonged to the mother and not to the researcher.

Secondly, the total dose of remifentanil varied depending on the length of labor and the number of applications provided by the mother. In the remifentanil-PCA method minimum interval between doses on the level of 2 min was specified, but the actual interval between successive doses in the method of PCA was dependent on the subjective perception of pain by the women giving birth. The time from the last dose of remifentanil to the moment of delivering the baby was also different, but in each case was longer than the half-life time of remifentanil. Taking into account that remifentanil has a very short half-life time, the listed limitations should not have any significant influence on our results and conclusions.

In conclusion, remifentanil PCA analgesia during labor in doses of 0.2 µg/kg, repeated not more frequently than every 2 min, does not significantly modify the hemoglobin oxygen saturation, heart rate and blood pressure in infants during the first day of life. Further studies are needed to explain the observed trend for arterial hypotension in the first hour of life in infants born to mothers treated with remifentanil.

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